Comparison of the Adrenal and Renal Responses to Angiotensin II in Fetal Lambs and Adult Sheep

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SUMMARY The adrenal and renal responses to similar increases in plasma angiotensin II (AII) were studied in chronically catheterized fetal lambs (112-131 days gestation; term 145 days) and adult nonpregnant sheep. The rate of AII infusion was adjusted to compare the effect of similar rises in plasma AII concentration between fetuses and adult ewes. Increases in plasma AII were associated with a decrease in plasma renin activity (PRA) in both fetuses (5.55 ± 1.53 to 2.11 ± 0.59 ng/ml per hr, \( P < 0.05 \)) and adult ewes (1.28 ± 0.34 to 0.62 ± 0.16 ng/ml per hr, \( P < 0.05 \)), but the percent changes in PRA for similar increases in plasma AII were not different when fetuses were compared to adult ewes. Contrary to the effect of AII on PRA, the increase in plasma AII did not produce parallel changes in plasma aldosterone concentration when fetuses were compared to adult ewes. The percent changes in plasma aldosterone concentration for similar increases in AII concentration were significantly higher in adult ewes (+165 ± 37%) than in fetuses (+58 ± 15%) \(( P < 0.01 \)). Finally, there were no significant changes in fetal urinary excretion of PGE and PGF2 \( \alpha \) when a significant rise \(( P < 0.05 \)) was observed in adult ewes at the highest level of plasma AII concentration. In summary, the present results tend to suggest that there are differences between fetuses and adult ewes in the response to AII, the response being smaller in fetuses.

Circ Res 50:140-147, 1982

THE ACTIVITY of the renin-angiotensin system has been found to be elevated during fetal life and in newborns when values are compared to adult levels (Mott, 1975). Factors controlling the activity of the renin-angiotensin system have also been investigated. It has been demonstrated that fetal plasma renin activity (PRA) and plasma angiotensin II (AII) levels increase after stimulation by furosemide (Siegel and Fisher, 1980), blood volume reduction (Robillard et al., 1979), fetal hypotension (Lumbers and Lewes, 1979), hypoxemia (Robillard et al., 1981), and aortic constriction (Smith et al., 1974). Conversely, inhibition of prostaglandin synthesis by indomethacin (Matson et al., in press), infusion of exogenous arginine vasopressin (Robillard and Weitzman, 1980a) and fetal hypertension during infusion of phenylephrine (Lumbers and Lewes, 1979) are associated with significant decreases in fetal PRA. However, previous attempts to study factors regulating aldosterone secretion during fetal life suggested that fetal aldosterone secretion “in vivo” is not controlled by ACTH (Brown et al., 1978), AII (Siegel and Fisher, 1980), nor variations in plasma potassium concentration (Wintour et al., 1979), despite the fact that, in vitro, the fetal adrenal gland has the ability to synthesize and secrete aldosterone (Pasqualini et al., 1966; Dufau and Villee, 1969; Wintour et al., 1977). On the other hand, we recently demonstrated a close correlation between fetal PRA and plasma aldosterone concentration, suggesting that aldosterone secretion is under the influence of the renin-angiotensin system during fetal life (Robillard et al., 1980b).

The present protocol was designed to study the role of AII in modulating aldosterone secretion and plasma renin activity during fetal life and to determine whether there are differences between fetal and adult responses to AII. Since the volume of distribution and plasma clearance rate of AII are unknown during fetal life and might be different than in adults, we compared the effects of similar plasma AII concentrations rather than comparing similar rates of infusion. Moreover, we determined the effects of similar increases in plasma AII concentration on renal blood flow, glomerular filtration rate, and excretion of water and electrolytes in fetal lambs and adult ewes. Finally, the effect of AII on urinary excretion of prostaglandins were compared between fetal lambs and adult ewes.
**Methods**

**Animal Preparation and Surgical Procedures**

Pregnant sheep of Dorset and Suffolk mixed breeding were obtained from a local source, and the gestational age was based on the induced ovulation technique, as previously described (Jennings and Crowley, 1972).

Anesthesia of the ewe and surgery of the fetus were performed as described previously (Robillard and Weitzman, 1980a), 6 days before doing any experiments. Before the start of each experiment, fetal weight was estimated according to the following formula: fetal body weight (kg) = \((0.096 \times \text{gestational age (days)}) - 9.223, (r = 0.85, P < 0.001)\) (Robillard and Weitzman, 1980a).

Adult nonpregnant ewes were also studied. Surgery was performed at least 6 days before experiments using the same procedures described for the fetus. A bladder catheter was introduced via the urethra the day of the experiment.

**Physiological studies**

During the physiological studies, each ewe was transferred into a small cart permitting it to stand only. Synthetic All (Beckman Instruments) was infused in 17 chronically catheterized fetal lambs between 112 and 131 days of gestation (term being 145 days) and in nine adult nonpregnant ewes. Prior to the infusion of All, a control infusion of 5% dextrose was administered intravenously for a period of 90 minutes in both fetuses and adult nonpregnant ewes at respective rates of 0.09 ml/min and 0.2 ml/min. After the control infusion period, All was infused at three different incremental rates, each one lasting 60 minutes, before any blood samples were taken; preliminary studies have demonstrated that an equilibration period of 45 minutes is sufficient to reach a steady plateau of plasma All in the fetus and adult nonpregnant ewe. In fetuses, All was infused at 25.8 ± 0.8, 47.6 ± 1.8, and 96.5 ± 4.1 ng/min per kg of body weight and in adult nonpregnant ewes at 5, 10, and 20 ng/min per kg of body weight. A bolus of All (20 ng/kg) was administered to either the fetus or adult nonpregnant ewes prior to the start of the continuous infusion; this dose was repeated before going to the continuous rate of infusion, and a double dose (40 ng/kg) was given before starting the third and last rate of All infusion.

In 15 fetuses and 7 adult nonpregnant ewes, glomerular filtration rate (GFR) was determined by a constant infusion of \(^{[125}\text{I}]-\text{sodium iothalamate}\) (Glofil, Abbott Laboratories) into the femoral vein prior to and during All infusion. A priming dose of 0.45 μCi/kg of iothalamate was administered, followed by a constant infusion of 0.1 μCi/kg per min in 5% dextrose solution. An equilibration time of 75 minutes was observed before the start of the first renal clearance. GFR was determined over a 15-minute period before the start of All infusion and just prior to the completion of each of the three incremental All periods. Urine was also collected for determination of urinary electrolytes (Na⁺, K⁺, Cl⁻) and prostaglandins (PGE and PGF2α) excretion rate, and urine osmolality.

Renal blood flow in fetuses and adult ewes was determined at the end of the control period and at the end of each of the three incremental All periods by infusing approximately 2.0 × 10⁶ radioactive microspheres (15 ± 3 μm) labeled with either \(^{141}\text{Ce},\ ^{85}\text{Sr},\ ^{46}\text{Sc},\ \text{or}\ ^{95}\text{Nb}\), as previously described (Heymann et al., 1977; Robillard and Weitzman, 1980a). Blood for lower body independent reference sample was collected from the femoral artery during a period of 3 minutes beginning 20 seconds before the injection of microspheres and at a withdrawal rate of 2.91 ml/min in fetuses and 4.81 ml/min in adult nonpregnant ewes using a Harvard infusion-withdrawal pump.

Arterial blood samples for determinations of arterial blood gases (Pco₂ and Po₂), pH, plasma All, aldosterone, renin activity, and electrolytes (Na⁺, K⁺, Cl⁻) concentrations and for hematocrit, total plasma proteins, plasma osmolality, and plasma \(^{[125}\text{I}]-\text{sodium iodothalamate}\) were drawn during the control infusion period and just prior to the completion of each of the three incremental All periods. Fetal blood was replaced with an equal amount of maternal blood after each sample was obtained to avoid any hemodynamic effects of sampling. In adult nonpregnant sheep, blood withdrawn for analysis was replaced with an equal amount of blood obtained from the same animal 24 to 36 hours prior to the experiment.

During each experiment, arterial blood pressure and fetal amniotic pressure were recorded continuously with Statham P23Db pressure transducers (Statham Instruments Div., Gould Inc.) and a Beckman R-611 recorder. Fetal mean arterial blood pressures (MABP) were corrected relative to concomitant amniotic pressures. Heart rate was monitored with a cardiotachometer triggered from the arterial pressure pulse wave.

**Analytical Methods**

Blood for pH, Pco₂, and Po₂, was collected anaerobically in heparinized glass syringes, and measurements were immediately determined with the appropriate pH, Pco₂, and Po₂ electrodes at 39°C using a Radiometer PHM 72 MK2 acid-base analyzer (Radiometer Co.). Plasma electrolytes (Na⁺, K⁺, Cl⁻), plasma osmolality, plasma protein content, and concentrations of \(^{[125}\text{I}]-\text{sodium iodothalamate}\) in plasma and urine were determined as previously described (Robillard et al., 1981).

All blood samples for plasma aldosterone and PRA measurements were collected, respectively, in heparinized syringes and in chilled tubes containing EDTA, kept on ice, and centrifuged within a few
minutes at 4°C. PRA and plasma aldosterone concent-
trations were determined by radioimmunoas-
says as described previously (Haber et al., 1969; Ito
et al., 1972; Robillard et al., 1980b).

Blood samples for plasma AII determinations
were collected in chilled tubes containing 0.3 m
EDTA and 0.025 m O-phenanthroline. Thereafter,
the cells and proteins were immediately precipi-
tated with acetone 65% and the supernatant dried
under air for subsequent chromatographic isolation
of AII on SP Sephadex in sodium acetate buffer.
AII then was measured by radioimmunoassay by
the method previously described by Catt et al.
(1974) and Cain et al. (1972). Cross-reactivity of the
AII antiserum based on AII as 100% reactive is
131% for angiotensin III and less than 3% for angio-
tensin I. In this assay the minimal dose detectable
averaged 2.89 ± 1.54 pg while the ED50 was 55.8 ±
7.6 pg (mean ± sd). The intra-assay coefficient of
variation averaged 5.7% and the interassay varia-
tion, 8.8%. The recovery of unlabeled AII (100–1000
pg) added to plasma was shown to be uniform (r =
0.989) over the range tested. Recoveries determined
by addition of known amounts of unlabeled AII
agreed well with recoveries determined by traced
method (49.1% vs. 51.3%).

Urine samples for prostaglandins determination
were collected under ice, then immediately frozen
at −70°C. Urine samples were extracted with eth-
ylacetate and separated into classes by silicic acid
chromatography. The urinary PGE and PGF2α
levels were determined by radioimmunoassay, using
specific antiserum. The technique, reliability, and
full characterization of each assay have been re-
ported previously (VanOrden et al., 1973, 1977).

Gamma emissions generated from the micro-
spheres were measured from fetal and adult kidneys
and from the reference femoral arterial blood
samples. Immediately after being removed from the
animal, the kidneys were weighed, cut into sagittal
sections of less than 1 g, and placed in counting
vials containing a predetermined amount of 10%
formalin in such a way as to prevent air tissue
interfaces that could alter the counts. Energy win-
dow ranges were set between 74 and 102 keV for
141Ce counts, 210–275 keV for 86Sr, 320–410 keV for
95Nb, and 420–580 keV for 46Sc. True 86Sr, 95Nb, and
141Ce counts were obtained by means of isotope
separation techniques and standard calculations
(Heymann et al., 1977).

Computations and Data Analysis

The plasma clearance rate of AII (PCR AII) was
calculated as previously described (Robillard and
Weitzman, 1980a): PCR AII (ml/min) = 0.491 x
AIIIR/PAII(−PAII), where AIIIR is the AII infusion
rate, and PAII, and PAII are plasma AII concen-
trations during control collection (i) and at equilib-
rium (f) during AII infusion, corrected for a mean
extraction efficiency of 49.1%.

Renal blood flow (RBF), renal vascular resist-
ance (RVR), and filtration fraction (FF) were de-
determined according to the following formula: RBF
(ml/min) = total kidney counts x reference flow
from the femoral artery (ml/min)/total femoral
blood counts; RVR (mm Hg/ml per min) = RPF/
RBF where RPP is the renal perfusion pressure
estimated to be equal to the aortic pressure minus
the inferior vena cava pressure; FF (%) = GFR/
RPF where GFR is the glomerular filtration rate
(ml/min) and RPF is the renal plasma flow (ml/
min), RPF being equal to RBFx(1-hematocrit).

In our statistical analysis, Student’s paired t-test
was used to compare data obtained before and
during AII infusion in the same animal, whereas
the differences between fetal lambs and adult non-
pregnant ewes were analyzed by a nonpaired t-test.
The term “significant” is used throughout the paper
to describe changes with a total P value of less than
0.05 in a two-sided significance limit. When multiple
comparisons were done on the same group of data,
the critical value of t was corrected using the Bon-
ferroni method (Wallenstein et al., 1980). The re-
results are presented as mean ± se.

Results

Plasma AII concentrations before and at three
different rates of infusion of AII are presented in
Figure 1. It is demonstrated that, to achieve similar
plasma AII concentrations in fetal lambs and adult
nonpregnant ewes (referred to as adult ewes in the
text), the rate of AII infusion had to be five times
higher in fetuses. It was also found that AII infusion
in fetuses did not alter maternal AII concentrations:
plasma AII levels increased from 58 ± 9 to 401 ± 14
pg/ml in fetuses, while it remained between 53 ± 5
and 43 ± 3 pg/ml in the pregnant ewes. The plasma
clearance rate of exogenous AII (PCR AII) did not
vary significantly during different rates of AII in-
fusion in either fetal lambs or adult ewes. However,
PCR AII values were always higher in fetuses than
in adult ewes at each level of AII infusion; the mean
values being, respectively, 170 ± 23 ml/min per kg

![Figure 1](http://circres.ahajournals.org/)

**Figure 1** Effect of AII infusion on plasma AII concen-
tration in fetal lambs (n = 17) and adult nonpregnant
ewes (n = 9). Values are mean ± SEM.
FETAL AND ADULT SHEEP RESPONSES TO ANGIOTENSIN II/Robillard et al.

TABLE 1  Control Blood Values for Fetal Lambs and Adult Nonpregnant Ewes

<table>
<thead>
<tr>
<th></th>
<th>Fetus (n = 17)</th>
<th>Adult ewe (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.37 ± 0.01</td>
<td>7.46 ± 0.02</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>44 ± 1</td>
<td>34 ± 1</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>24 ± 1</td>
<td>101 ± 3</td>
</tr>
<tr>
<td>Na⁺ (mEq/liter)</td>
<td>144 ± 1</td>
<td>143 ± 1</td>
</tr>
<tr>
<td>K⁺ (mEq/liter)</td>
<td>4.2 ± 0.2</td>
<td>4.1 ± 0.1</td>
</tr>
<tr>
<td>Cl⁻ (mEq/liter)</td>
<td>104 ± 1</td>
<td>108 ± 2</td>
</tr>
<tr>
<td>Osmolality</td>
<td>290 ± 2</td>
<td>287 ± 2</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>31 ± 1</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>Total proteins (g/100 ml)</td>
<td>3.8 ± 1</td>
<td>6.6 ± 0.3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

in fetuses and 37 ± 3 ml/min per kg in adult ewes (P < 0.01).

There were no significant changes in arterial blood gases (P<sub>CO₂</sub> and P<sub>AO₂</sub>), pH, plasma concentrations of electrolytes (Na⁺, K⁺, Cl⁻), plasma osmolality, hematocrit, and plasma total protein concentrations when control values in both fetal lambs and adult ewes (Table 1) were compared to values obtained during different rate of AI infusion.

**Effect of Angiotensin II Infusion on Plasma Renin Activity (PRA) and Plasma Aldosterone Concentration**

The increase in plasma AI concentration was associated with a significant decrease in PRA in both fetuses and adult ewes (Fig. 2): PRA decreased from 5.55 ± 1.53 to 2.11 ± 0.59 ng/ml per hr (P < 0.05) in fetuses and from 1.28 ± 0.34 to 0.62 ± 0.16 ng/ml per hr (P < 0.05) in adult ewes. However, there was no significant difference in the percent changes in PRA for similar increases in plasma AI concentrations when fetuses were compared to adult ewes (Fig. 2). At the highest level (level III) of plasma AI concentration, PRA was decreased by 50.8 ± 8.1% in fetuses and 47.2 ± 6.8% in adult ewes (P < 0.1).

Contrary to the effect of AI on PRA, the increase in plasma AI concentration did not produce parallel changes in plasma aldosterone concentration when fetuses were compared to adult ewes (Fig. 3). The rise in plasma aldosterone following a similar steplike increase in plasma AI concentration was observed earlier in adult ewes than in fetuses; plasma aldosterone increased from 63 ± 17 to 133 ± 49 pg/ml in adult ewes, while no changes were seen in fetuses following the first increase in plasma AI concentration (level I) (Fig. 3). Moreover, the percent changes from baseline to peak (level III) for plasma aldosterone were significantly higher in adult ewes (+165 ± 37%) than in fetuses (+58 ± 15%) (P < 0.01).

**Effect of Angiotensin II Infusion on Fetal Renal Function, Urinary Excretion of Prostaglandins (PGE and PGF<sub>2α</sub>) and Renal Hemodynamics**

There were no significant changes in urinary flow rate and glomerular filtration rate during infusion of AI in either fetuses or adult ewes (Table 2). Significant rises in urine osmolality and urinary Na⁺ and Cl⁻ excretion were observed at the highest level of plasma AI concentration (level III) in both fetuses and adult ewes. No significant changes were seen in urinary potassium excretion rate.

The effect of an increase in plasma AI concentration on urinary prostaglandins excretion is presented in Table 2. No significant changes were found in fetuses, but significant rises in urinary PGE and PGF<sub>2α</sub> were observed in adult ewes after reaching the highest level of plasma AI concentration (level III).

The effect of AI on renal hemodynamics was studied in six fetuses and three adult nonpregnant...
ewes. Rise in plasma All concentration (level III) was associated with a significant decrease in fetal renal blood flow (RBF) from 39.5 ± 6.0 to 18.4 ± 2.4 ml/min (P < 0.01), and significant increases in renal vascular resistance (RVR) from 2.12 ± 0.18 to 2.31 ± 0.21 mmHg/ml per min (P < 0.05) and filtration fraction (FF) from 5.7 ± 0.7 to 11.5 ± 0.7% (P < 0.01). Similarly, RBF decreased from 590 ± 82 to 443 ± 82 ml/min, and RVR and FF increased with All infusion as presented in Table I. V, urinary flow rate; Cioth, clearance of [125I]sodium iothalamate; Uosm, urine osmolality; UV, urinary excretion rate, n = number of animals. Values are mean ± SEM.

| Table 2 The Effect of All on Renal Function in Fetal Lambs and Adult Ewes |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Fetal lamb       | Adult ewe       |                 |                 |                 |                 |                 |                 |
|                 | Plasma All conc. |                 |                 |                 |                 |                 |                 |                 |
|                 | V (ml/min)        |                 |                 |                 |                 |                 |                 |                 |
| Level I         | 15               | 0.59 ± 0.07     | 0.55 ± 0.06     | 0.58 ± 0.07     | 0.62 ± 0.08     | 7.92 ± 0.13     | 1.23 ± 0.18     | 1.46 ± 0.25     | 2.53 ± 0.85     |
| Level II        | 15               | 2.12 ± 0.18     | 2.27 ± 0.15     | 2.31 ± 0.21     | 2.37 ± 0.21     | 7.67 ± 11      | 82 ± 9          | 82 ± 11         | 73 ± 9          |
| Level III       | 15               | 23.85 ± 4.18    | 27.25 ± 5.49    | 33.01 ± 7.26    | 42.02 ± 7.13*   | 7.39 ± 18      | 74 ± 30         | 78 ± 24         | 261 ± 93*       |
|                 | Ucr V (µEq/min)  |                 |                 |                 |                 |                 |                 |                 |
| Level I         | 15               | 13.69 ± 2.63    | 16.32 ± 3.46    | 20.18 ± 4.74    | 28.86 ± 5.47*   | 7.58 ± 27      | 80 ± 29         | 106 ± 25        | 297 ± 91*       |
| Level II        | 15               | 8.89 ± 2.94     | 7.93 ± 2.62     | 7.28 ± 2.41     | 7.60 ± 2.70     | 7.17 ± 19      | 143 ± 28        | 144 ± 21        | 150 ± 35        |
| Level III       | 15               | 136 ± 14        | 157 ± 18        | 166 ± 18        | 179 ± 18*       | 7.737 ± 65     | 652 ± 81        | 626 ± 106       | 436 ± 58*       |
|                 | UcrF V (ng/min)  |                 |                 |                 |                 |                 |                 |                 |
| Level I         | 15               | 0.82 ± 0.12     | 0.98 ± 0.13     | 0.90 ± 0.13     | 1.06 ± 0.13     | 5.28 ± 0.63    | 3.28 ± 0.72     | 3.97 ± 0.61     | 6.47 ± 0.84*    |
| Level II        | 15               | 0.88 ± 0.12     | 0.99 ± 0.12     | 0.85 ± 0.11     | 0.94 ± 0.12     | 5.394 ± 1.57   | 4.82 ± 2.05     | 5.98 ± 2.44     | 8.33 ± 2.16*    |

* For P < 0.05 when values during All infusion are compared to control values. Values for plasma All concentration for control and levels I, II, and III as presented in Table 1. V, urinary flow rate; Cioth, clearance of [125I]sodium iothalamate; Uosm, urine osmolality; UV, urinary excretion rate, n = number of animals. Values are mean ± SEM.

Discussion

The results of the present study demonstrate that All: (1) produces a similar decrease in PRA in both fetal lambs and adult ewes, (2) stimulates aldosterone secretion to a lesser degree during fetal life than after birth, and (3) does not stimulate production of renal prostaglandins (PGE and PGF₂α) during fetal life.

It is also demonstrated that the plasma clearance rate of All is about 5 times higher in fetuses than in adult ewes. Factors that might account for this difference have not yet been investigated. However, large plasma volume (Creasy et al., 1970), low protein concentration (Table 1), and possible high angiotensinase activity (Talledo, 1967) in fetuses, compared to adult animals, may be responsible for the difference in plasma clearance rate of All.

Influence of Increase in Plasma All Concentration on Fetal PRA and Plasma Aldosterone Concentration

It is demonstrated in the present study that the sensitivity of the fetal kidney to elicit a decrease in renin secretion following a rise in plasma All concentration is similar to that of adult ewes. A previous study by Iwamoto and Rudolph (1981) also suggests that All inhibits renin secretion in fetal lambs between 100 and 138 days gestation.

Factors responsible for the decrease in fetal PRA following a rise in plasma All concentration have not been investigated. However, it is unlikely that an increase in plasma aldosterone concentration directly affects renin secretion. In previous studies of adult animals (Geelhoed and Vander, 1967), the investigators have been unable to identify a direct action of aldosterone on renin secretion unless the rise in circulating mineralocorticoids was associated with an increase in total body sodium (Robb et al., 1969), which is unlikely in the present study. More likely, the decline in fetal PRA observed in the present study may be secondary either to a direct action of All on the juxtaglomerular cells, as previously suggested in adult animals (Shade et al., 1973; McDonald et al., 1975), or to an increase in fetal renal perfusion pressure, or both. In the present study, the decline in fetal PRA following the first increase in plasma All concentration (level I) is associated with an 8 ± 1% rise in fetal arterial blood pressure.

The present study also demonstrates that All can stimulate aldosterone secretion during the last trimester of gestation in fetal lambs. Previous in vitro studies have shown in humans (Pasqualini et al., 1966; Dufau and Villee, 1969) and sheep (Wintour et al., 1977) that the fetal adrenal gland is able to synthetize and secrete aldosterone very early in gestation. However, previous attempts to study factors regulating aldosterone secretion during fetal
life suggested that the renin-angiotensin system does not have a predominant role, if any, in controlling aldosterone secretion (Alexander et al., 1968; Siegel and Fisher, 1980). Moreover, it was also demonstrated that an increase in plasma potassium concentration (Wintour et al., 1979) and ACTH infusion (Brown et al., 1978) cannot induce a significant rise in fetal plasma aldosterone concentration.

The reasons for the differences between the previous studies (Alexander et al., 1968; Siegel and Fisher, 1980) and the present results are difficult to explain. Since plasma AII concentrations were not determined in any of the previous studies (Alexander et al., 1968; Siegel and Fisher, 1980), one may speculate that the rise in plasma AII following stimulation of the renin-angiotensin system was not important enough to produce a significant increase in plasma aldosterone concentration. Moreover, it is also possible that the time period allowed for stimulation of the fetal adrenal gland following a rise in plasma AII concentration (Siegel and Fisher, 1980) might have been too short to permit observation of any significant changes in plasma aldosterone. Finally, the increase in fetal plasma aldosterone concentration, seen in the present study, cannot be explained by placentation from mother to fetus, since there was no evidence of an increase in maternal plasma AII concentration during AII infusion.

However, despite the fact that the fetal adrenal gland has the ability to secrete aldosterone in response to AII, the percent changes in plasma aldosterone concentration were smaller in fetuses than in adult ewes following similar rises in plasma AII concentration. These results suggest that the fetal adrenal gland is not fully sensitive to AII. Factors explaining this low adrenal sensitivity to AII during fetal life, compared to that of adult sheep or newborn lambs (Siegel, 1981), have not yet been investigated. Previous studies in adults (McCaa et al., 1973; Sealey et al., 1978) suggested that basal plasma AII levels may determine the ability of the adrenal to secrete aldosterone following AII stimulation. However, there is no evidence that the lowest aldosterone-stimulating effect of AII in the fetus compared to adult animals is secondary to low endogenous levels of AII, the basal level for plasma AII concentration being similar in both fetuses and adult ewes. One also may speculate that the enzymatic potential for aldosterone biosynthesis and the number of cellular receptor sites and receptor binding affinity for AII are low during fetal life and might increase during the process of maturation, as suggested previously for the fetal adrenal receptors for ACTH (Durand, 1979). Finally, it is also possible, as suggested in adult (Catt et al., 1979), that the state of sodium homeostasis, which is different in the fetus than in the newborn or adult animal (Ziegler and Fomon, 1974), may also have a role to play in the adrenal sensitivity to AII during fetal life.

Effect of Angiotensin II on Fetal Renal Function, Renal Prostaglandins Excretion, and Renal Hemodynamics

Previous studies in adult animals have shown that both intravenous and intraarterial infusion of AII may produce moderate to marked decreases in renal blood flow and lesser decreases or no changes in GFR (Navar and Langford, 1974; Levens et al., 1981). Moreover, it has been demonstrated that the effects of AII infusion on urinary flow rate and sodium excretion are dose-dependent: both an antidiuretic and antinatriuretic effect and a diuretic and natriuretic effect have been reported during low and high rate infusion of AII, respectively (Levens et al., 1981).

In the present study, the effects of an increase in plasma AII concentration on renal hemodynamics, GFR, and urinary sodium excretion are similar in both fetuses and adult ewes. Also, since the reduction in RBF is associated, in both groups of animals, with an increase in filtration fraction without changes in GFR, one may suggest that AII acts primarily by increasing the efferent arterial tone, and that this mechanism is functional even before birth. Finally, the increase in sodium and chloride excretion at the highest level of plasma AII concentration (level III) probably is a reflection of an increase in blood pressure and represents pressure natriuresis.

The absence of a rise in fetal urinary prostaglandin excretion following an increase in plasma AII concentration differs from what was found in adult nonpregnant ewes and from previous results in adult dogs (Dunn et al., 1981). The absence of changes in fetal urinary prostaglandins following a rise in plasma AII concentration is probably not secondary to a defect in the ability of the fetal lamb kidney to synthetize prostaglandin. Pace-Asciak (1977) in fetal lambs and Terragno and coworkers (1978) in fetal pigs demonstrated that the biosynthetic capacity of the fetal kidney for prostaglandins (PGF2α, PGE2, and PGI2) is mature during the last trimester of gestation. It is possible that the absence of an increase in fetal urinary prostaglandin excretion may be secondary to a smaller amount of AII perfusing the fetal kidney when compared to adult. Since the renal blood flow is significantly \( P < 0.005 \) lower in fetuses (1.92 ± 0.13 ml/min per g of kidney) than in adult ewes (4.20 ± 0.73 ml/min per g of kidney), the absolute amount of AII perfusing the fetal kidney will be less than in adults for similar plasma AII concentrations. Finally, one may speculate that the binding of AII to receptor in renomedullary interstitial cells (Brown et al., 1980) is decreased during fetal life, compared to adults, but this hypothesis still needs to be tested.

In summary, the present data support the idea
that ALL is an important modulator of plasma renin activity, plasma aldosterone concentration, and blood pressure during fetal life. However, the adrenal and vasopressor responses to a rise in plasma ALL concentration were less in fetuses than in adult ewes. Furthermore, the data demonstrate that ALL does not induce a rise in fetal urinary prostaglandin excretion at plasma levels known to increase renal prostaglandin production in adult ewes. Finally, the present results suggest that ALL may modulate fetal GFR by controlling the efferent arteriolar tone, as previously suggested for adult animals (Hall et al., 1977).

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Circ Res. 1982;50:140-147
doi: 10.1161/01.RES.50.1.140

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
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